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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Philip L. McGarrigle
Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051

EXAMINER
ZITOMER, STEPHANIE W

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/689,937	CHRISTIANS ET AL.	
	Examiner	Art Unit	
	Stephanie Zitomer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application status

1. Applicant's election without traverse of Invention I, claims 1-49 (*sic* 48) in Paper No. 6 filed September 21, 2001 is acknowledged. Claims 50-69 have been withdrawn as being directed to nonelected inventions.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). Notably, the provisional applications 60/162,739 and 60/191,345 filed October 30, 1999 and March 22, 2000, respectively, do not provide written description support under 35 USAC 112, first paragraph, for the presently claimed methods employing a "bait molecule", for claimed methods of preparing nucleic acids other than prokaryotic mRNAs or for such methods employing bait molecules modified with "selectable elements".

Informalities

3. The disclosure is objected to because of the following informalities:

(a) At pages 20-23 of the specification a colon (:) appears in place of the "micro" symbol, μ.

(b) In claim 6, the period improperly placed inside the parentheses should be moved to come after the parentheses.

(c) In claim 42, γ-S-ATP is written as (-S-ATP.

Appropriate correction is required.

Rejection under 35 U.S.C. 112, first paragraph: Lack of written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13, 17-27, 31 and 34-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of preparing a nucleic acid in which a "bait molecule" is capable of complexing specifically with a target sequence whereby the bait molecule:target sequence may be removed from a population of nucleic acids. The phrase "bait molecule" which is not defined in the claims or in the specification encompasses a large genus of bait molecule species. The specification states at page 10, lines 4-15, that the bait sequence may be DNA even though the bait molecule was not previously identified as a "sequence" and at page 11, lines 20-23 and page 12, lines 7-11, an antibody to DNA:RNA hybrids or to rRNA is mentioned as a non-nucleic acid bait molecule. However, only use of the former is described. In view of the diverse nature of species of the genus of claimed "bait molecules", nucleic acid and antibody cannot be considered representative of the genus. Other potential bait molecules encompassed by the claimed genus may be mentioned, for example, aptamers, nucleic acid binding proteins, cationic polymers, triplex-forming nucleic acids and intercalating agents all of which and each of which comprise a myriad of different chemical structures. None of these or other species or the aforementioned antibody is identified in the specification nor is it taught how to use these species in the claimed invention method. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. In view of the failure of the specification to identify and teach how to use a representative number of "bait molecule" species, one of skill in the art at the time the claimed invention was filed would not have recognized that applicant was in possession of the claimed "bait molecule" genus. This rejection may be overcome by amending the claims to identify the "bait molecule" as nucleic acid.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claim are confusing in the apparent random mixing of "bait molecule" in which "bait" is an adjective and "bait" in which "bait" is a noun. It is suggested to always use "bait molecule" for consistency and clarity.

(b) The claims are confusing in the recitations "contacting" which is not an active method step and "is capable of complexing" which recites a property of the bait molecule. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter the claims encompass as well as make clear the subject matter from which others would be precluded. *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested to make "contacting" active by reciting a result, e.g., the bait molecule --complexes-- a target sequence.

(c) The recitation "capable of" is confusing in other contexts, e.g., claims 22, 23 and 25, because it is unclear whether a method step or property is intended. It is suggested to delete "capable of" and render "binding" in these claims in the active form --binds--.

(d) Claims 1-44 lack antecedent correspondence between the last steps in claim 1, "fragmenting" and "adding a signal moiety to the fragment" with the preamble "preparing a nucleic acid". It is suggested to amend the preamble to recite appropriate antecedent basis for the last steps, e.g., to recite "preparing nucleic acid probes"..

(e) Claims 3-5 and 47-45 are rendered indefinite by the recitation "derived from" which is an indeterminate phrase and is not defined in the claims or in the specification. It is suggested to delete "derived".

(f) Claim 7 is confusing in the recitation "stable RNA" which is not defined in the claims or in the specification. The statement at page 9, lines 12-13, that "[i]n a preferred

embodiment the target sequences are stable RNAs including rRNA and tRNA" (emphasis added) does not indicate the scope of "stable RNAs" such that one of skill in the art would be reasonably apprised of the scope of the invention. It is suggested to clarify the recitation.

(g) Claims 13, 14 and 16 lack antecedent basis in claim 1 for "cloned from single stranded phage DNA" and "synthesized by reverse transcriptase", respectively, because both recitations refer to a bait molecule that is a nucleic acid whereas claim 1 does not recite a nucleic acid bait molecule. It is suggested to provide appropriate antecedent basis in claim 1.

(h) Claim 25 lacks antecedent basis in claims 22, 20 or 1 because none of the latter claims recites a selectable element that one of skill in the art would expect to be bound by streptavidin (*sic* streptavadin). It is suggested to provide an appropriate antecedent in one of the latter claims.

(I) Claims 26 and 27 lack antecedent basis in any of claims 22, 20 and 1 for "said RNA sequence". It is suggested to provide appropriate antecedent in one of the latter claims.

(j) Claims 20 and 28-30 are confusing in that "exposing" and "reagent which specifically recognizes" are *non sequitur* to "to form a...complex" in claim 22 and "removing" in the latter claims. It is suggested to rewrite claims 20 and 28 in active form which accomplishes forming a complex and "removing".

(k) Claim 29 is confusing because it lacks antecedent basis in claim 28 because RNAse H is known to digest RNA in an RNA:DNA hybrid but is not known to "remove" the hybrid. It is suggested to clarify.

(l) Claims 31-37 are confusing because removing the target first and the bait thereafter is *non sequitur* to claim 1 in which the target and bait molecule are removed as a complex. Clarification is suggested.

(m) Claim 35 is confusing because it is unclear whether the bait molecule is recovered from the bait molecule:target complex and reused. Cf. above at (l) regarding claim 31. Clarification is suggested.

(n) Claim 36 lacks antecedent basis in claims 35, 34, 31 and 1 because none of the latter claims recites an RNA which the RNAse would be expected to digest. It is suggested to provide antecedent basis.

(o) Claims 38-44 are confusing in the recitation "said signal moiety is a biotin" because biotin was known in the art as a ligand or member of an affinity pair, not a signal-generating molecule. Furthermore, biotin is described in the specification as "for staining with labeled streptavidin conjugate" (page 17, line 13) and in the experimental section as a mobility-shift facilitator when conjugated with avidin (pages 24-26). It is suggested to clarify claims 1 and 38, for example, by changing "signaling moiety" to --label-- as used at pages 15 and 16.

(p) Claim 39 is rendered indefinite by the abbreviation "PEO" which may represent more than one word sequence. It is suggested to recite the appropriate words represented by "PEO".

(q) Claim 11 is confusing in that it is unclear in relation to what the bait molecule is "exogenously generated". Clarification is suggested, e.g., specifying that the bait molecule is generated from a population of nucleic acids that are unrelated to the nucleic acids of interest.

(r) Claims 41 and 42 lack antecedent basis in claim 40 for the chemical modification of the 5' ends of the fragments because in claim 40 the signal moiety is already attached to the 5' ends of the fragments. Therefore, it is unclear why/how the 5' ends are chemically modified in claims 41 and 42. It is suggested to change the dependency of claim 41 to claim 1.

(s) Claim 43 lacks antecedent basis in claim 40 for "said chemical modification". It is suggested to change the dependency of claim 43 to claim 42.

Rejections under 35 U.S.C. 102: Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 45 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by the patent to Hornes et al. (5,759,820 issued June 2, 1998). Hornes et al. discloses the claimed invention method of increasing the relative percentage of a population of nucleic acids of interest in a mixed population of nucleic acids comprising (a) contacting a nucleic acid sample with a bait molecule that is capable of hybridizing specifically to a target sequence but not to sequences in the population of interest such that a bait molecule:target sequence complex is formed; (b) removing the bait molecule:target sequence complex wherein the nucleic acid sample is an RNA sample (column 7, lines 7-13).

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 45-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Alland et al. (2001/0049094 A1 filed on October 23, 1998). Alland et al. discloses the claimed invention method of increasing the relative percentage of a population of nucleic acids of interest in a mixed population of nucleic acids comprising (a) contacting a nucleic acid sample with a bait molecule that is capable of hybriding specifically to a target sequence but not to sequences in the population of interest such that a bait molecule:target sequence complex is formed; (b) removing the bait molecule:target sequence complex wherein the nucleic acid sample is an RNA sample derived from a gram negative prokaryotic organism (page 2, paragraph 0012).

Rejections under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alland et al. (US 2001/0049094 A1) as applied to claims 44-47 above (paragraph 7) in view of Fisher et al. (5,643,761) and further in view of Hornes et al. (5,759,820) as applied to claims 44 and 46 above (paragraph 6). Alland et al. discloses a method for increasing the relative percentage of a population of nucleic acids of interest in a mixed population of nucleic acids which is essentially the same as that of claim 1 and comprises (a) contacting a nucleic acid sample with a bait molecule that is capable of complexing specifically to a target sequence; (b) removing the bait molecule:target sequence complex; and (c) selecting nucleic acid fragments from the resulting population of nucleic acids of interest (page 2, paragraph 0012; page 9, claims 6 and 7) which fragments are labeled (page 3, paragraph 0018). The claimed invention method differs from that of Alland et al. wherein the nucleic acids in the population of interest are fragmented after steps (a) and (b) whereas the reference nucleic acids are fragmented (provided as a library) prior to these steps. However, it would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to choose fragmenting before or after the method steps according to preference, desired results and experimental parameters. For example, where it was desired to have probes of a size smaller than the reference library inserts the skilled practitioner in the art would have been motivated to fragment the nucleic acids of interest after the method steps. The court determined in *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) that selection of any order of process steps is *prima facie*

obvious in the absence of new or expected results. It would have been further obvious and one of ordinary skill in the art would have been motivated to add a signaling moiety to the fragments according to intended use. For example, Alland et al. teaches using the selected fragments as probes for detecting nucleic acids in a sample (page 3, paragraph 0014) wherein alternative to providing a signaling moiety to the sample nucleic acids it was routinely practiced in the art to add a signaling moiety to the probe fragments.

Regarding claims 2-4, Alland et al. discloses that the nucleic acid sample is an RNA sample derived from a gram negative prokayotic organism (page 2, paragraph 0012, lines 13-17).

Regarding claim 5, Alland et al. does not disclose that the nucleic acid sample is derived from *E. coli*. However, it would have been obvious at the time the claimed invention was made and one of ordinary skill in the art would have been motivated to derive the nucleic acid sample from *E. coli* because this microbe was well studied and routinely used in the art for this reason. For example, Hornes et al. cloned the subtracted cDNA library in *E. coli* (column 15, lines 12-27) such that as would have been known to one of ordinary skill in the art the nucleic acids would be in condition for use in further subtractions of other nucleic acid samples.

Regarding claims 6-8, Alland et al. discloses that the population of interest is mRNA and the target sequence is rRNA (page 2, paragraph 0012, lines 13-17 and 23-24). According to the instant specification (page 9), "stable RNA" includes rRNA.

Regarding claims 9 and 10, Alland et al. discloses that the target rRNA is 23S or 16S RNA (page 4, paragraph 0033).

Regarding claims 11 and 12, Hornes et al. teaches exogenous generation of bait molecules by chemical synthesis (column 11, Example 4; column 15, lines 6-9). It would have been obvious and one of ordinary skill in the art the time the claimed invention was made would have been motivated to synthesize the bait molecule probes of Alland et al. by chemical synthesis in view of the teaching in the latter reference that the sequence of the entire *M. tuberculosis* genome was known and relied on (page 3, paragraph 0022) and further in view of the known benefit of ease and reduction in time and labor.

Regarding claim 13, Alland et al. does not disclose cloning bait molecules from single stranded phage DNA. However, in a subtraction method similar to that of Alland et al., Fisher et al. teaches preparing bait molecules by cloning in the single stranded phage, lambda (column 5, lines 62-65). It would have been obvious and the skilled practitioner in the art would have been motivated to prepare bait molecules by cloning from single stranded phage DNA by the teachings of Fisher et al. that phage vectors avoid problems of contaminating plasmids, attain high titer libraries, avoid the laborious work of subcloning DNA inserts into plasmids and phage cloning kits are commercially available (column 38, lines 38-65).

Regarding claims 14 and 16, Alland et al. does not disclose synthesizing bait molecules by reverse transcription using target sequence as template. However, Fisher et al. teach synthesis of bait molecules (driver library) by reverse transcription of target templates (column 3, line 49-column 36, line 2). It would have been obvious and the skilled practitioner in the art would have been motivated to reverse transcribe rRNA as an alternative to preparing bait molecules by PCR of rRNA 16S and 23S genes as in Alland et al. (page 4, paragraph 0033) using primers to 16S and 23S rRNA according to preference, available materials and desired experimental results in the absence of expected results or of evidence to the contrary.

Regarding claim 15, Alland et al. discloses the method of claim 1 wherein the nucleic acid sample is RNA, the bait molecule is DNA and the bait molecule:target complex is a DNA:RNA hybrid (page 9, claim 5; page 4, paragraph 0033, lines 8-9).

9. Claims 17-44 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alland et al. (US 2001/0049094 A1 filed October 23, 1998) in view of Fisher et al. (5,643,761) and Hornes et al. (5,759,820) as applied to claims 1-16 above (paragraphs 6-8) and further in view of Li et al. (5,759,778) and Joyce et al. (5,807,718). Regarding claims 17-19, Hornes et al. teaches the claim 1 method steps (a) and (b) embodiment wherein the bait molecule is attached to a solid substrate (column 8, lines 28-30).

Regarding claims 20 and 21, Fisher et al. teaches modification of the bait molecule with a selectable element which is the haptenic group, biotin (column 36, lines 52-60). Hornes et al. teaches modification of probes with biotin (column 5, lines 50-53).

Regarding claims 22-26, Alland et al in view of Fisher et al. does not specifically disclose the claim 20 method embodiment of claim 22 wherein the bait molecule:target complex is exposed to a reagent capable of binding the selectable element to form a reagent:bait molecule:target complex or the embodiments of claims 23-25 wherein the reagent is a ligand, the selectable element is biotin and the reagent is streptavidin, respectively. However, the use of affinity pairs for separation of nucleic acids was routinely practiced in the art, particularly with the biotin-avidin pair as taught by Li et al.. In a nucleic acid subtraction method similar to those of Alland et al., Fisher et al. and Hornes et al., Li et al. teaches the use of a haptenylated bait probe wherein the hapten is a molecule that is recognized and bound by another molecule such as an antibody and wherein the hapten may be an antigen, biotin, dinitrophenol, etc.(column 7, lines 59-66).

Regarding claims 26 and 27, Li et al. teaches that removing the nucleic acid is accomplished by separating the reagent:probe:target complex from the mixed population of nucleic acids containing the nucleic acid of interest wherein the complex is attached to a solid support (column 8, lines 15-36). Similarly, Hornes et al. teaches removal of hybrids by separating the probe:target complex from the mixed population of nucleic acids (column 7, lines 61-65). Alland et al. also teaches separation of hybrids by adding streptavidin coated beads to hybrids comprising biotinylated nucleic acids (page 4, paragraph 0037).

Regarding claims 28-30, Hornes et al. teaches removing RNA:DNA hybrids with a reagent that specifically recognizes the hybrids wherein the reagent is RNAse H (column 1, lines 59-64). As to the embodiment of claim 30, Li et al. teaches that the hybrid may be removed with an antobody (column 7, lines 60-63).

Regarding claims 31 and 34, Hornes et al. teaches removing the bait molecule:target sequence complex in two steps, removing any remaining bait molecules after target removal and repeating steps (a) and (b) of the method (column 8, line 54-column 9, line 5). Furthermore, the court determined in *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) that selection of any order of process steps is *prima facie* obvious in the absence of new or expected results.

Regarding claims 32 and 33, in a subtraction method similar to those of Alland et al., Fisher et al. and Hornes et al., Li et al. teaches using DNA nucleases for removal of

single stranded DNA from double stranded nucleic acids wherein the nucleases may be mung bean nuclease or Bal-31 nuclease (column 9, line 62-column 10, line 27). It would have been obvious to one of ordinary skill in the art to select the single stranded DNA degrading enzyme from among those known in the art including DNAse I based on considerations including preference, desired experimental results, available materials and cost in view of the noncriticality of the means for removal in the method of claim 1.

Regarding claim 37, Alland et al. teaches performing step (a) at a first temperature and step (b) at a second temperature (page 4, paragraph 0037).

Regarding the claim 1 method embodiment of claim 38 wherein the signaling moiety is biotin, biotin was routinely employed in the art as a means for attaching a signaling moiety to a nucleic acid. For example, Fisher et al. teaches modification of the bait molecule with biotin (column 36, lines 52-60) and Hornes et al. teaches modification of probes with biotin (column 5, lines 50-53).

Regarding claims 39-44, the signal moiety is PEO-Iodoacetyl Biotin and the kinase method steps for attaching it to nucleic acid fragments are recited. It would have been obvious and the skilled practitioner in the art would have been motivated to employ PEO-Iodoacetyl Biotin because it was commercially available with instructions for the obvious benefit of ease of use including time and labor saving. The kinase method of making biotinylated nucleic acids was known in the art, for example, as taught by Joyce et al. in a method of selecting nucleic acids from a sample nucleic acid population wherein the iodoacetyl biotin was carried on a hexylenediamine linker. However, the PEO linker was also known in the prior art and the choice of one linker or the other would have been motivated by preference, desired experimental results and available materials.

Regarding claim 49, Alland et al., Fisher et al. and Hornes et al. do not disclose that the nucleic acid sample is derived from *E. coli*. However, it would have been obvious at the time the claimed invention was made and one of ordinary skill in the art would have been motivated to derive the nucleic acid sample from *E. coli* because this microbe was well studied and routinely used in the art for this reason. For example, Hornes et al. cloned the subtracted cDNA library in *E. coli* (column 15, lines 12-27) such that as would have been

known to one of ordinary skill in the art the nucleic acids would be in condition for use in further subtractions of other nucleic acid samples.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact Patent Analyst Tiffany Tabb at 703-605-1238.

Stephanie Zitomer, Ph.D.

September 3, 2002

STEPHANIE W. ZITOMER
PRIMARY EXAMINER